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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
WALICKA, MALGORZATA A

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Applicati n N .	Applicant(s)	
	09/674,738	MAURER ET AL.	
	Examiner	Art Unit	
	Małgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- *Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.*
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: copies of papers used in 102 and 103 rejection.

The Response to restriction Requirement filed on Oct. 21, 2002 as paper No. 14 is acknowledged. Claims 1-6 are pending in the application and are the subject of this Office Action.

DETAILED ACTION

1. Election/Restriction

Applicant's election with traverse of the bromelain protease as characterized in Claim 1 part a), in Paper No. 14, is acknowledged. The traversal is on the ground(s) that "Applicants do not believe this restriction requirement is proper" (Remarks, line 5).

Upon reconsideration of the restriction requirement the examiner found the Applicants' traverse persuasive. The restriction requirement made in the previous Office Action, paper No. 13 is withdrawn; the new restriction requirement is as follows.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.

The species are as follows:

1. the bromelain protease as characterized in Claim 1 part a),

2. the bromelain protease as characterized in Claim 1 part b), and

3. the bromelain protease as characterized in Claim 1 part c).

Upon the allowance of a generic claim, Applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include

all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Claims 1-6, directed to the use of bromelain protease as characterized in Claim 1 part a) are the subject of This Office Action.

2. Objection

The title and disclosure are objected to for the spelling error in the name of the proteases which use is claimed. The correct spelling is bromelain not bromelaine; see the inventor's article by Harrach et al., included in IDS.

The quotation of the paper published in Journal of Protein Chemistry, 1995, 14, 41-52, is wrong throughout the specification. The first author on this paper is Tibor Harrach and not Klaus Eckert.

The specification is replete with spelling, grammar and typographical errors, e.g., page 3, line 16, "It has shown " should be "It has been shown"; page 9, line 25, "over night" should be "overnight".

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

3. Rejections

3.1. 35 USC section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 provide for the use of bromelaine proteases for inhibiting blood coagulation, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim 1-4 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

3.2. 35 USC section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3.2.1 Lack of written description

Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 6 is directed to a medicament containing bromelain protease that is a recombinant protease. The specification fails to disclose cloning and sequencing genes encoding proteases recited in part a), b) and c) of claim 1, the procedures necessary as the first step in obtaining these proteases in a recombinant form. The search done by examiner indicates that the genes encoding proteases to be used in the claimed invention have never been cloned by the inventors. Therefore, one skilled in the art is not convinced that the inventors, at the time the application was filed, had possession of the claimed invention.

3.2.2. Lack of enablement

Claim 1-6 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to the use of three bromelain proteases for inhibiting blood coagulation. The enzymes are identified by three features:

1) molecular weight,

2) optimal activity range,

3) the known 20 amino acid fragment of the unknown amino acid sequence.

The specification, however, fails to teach how to isolate and characterize the bromelain proteases so that they have properties as recited in claim 1, said properties to be used for inhibiting blood coagulation. Therefore, to make and use the claimed invention undue experimentation is necessary.

Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses three proteases isolated from so-called stem bromelain protease. Each of the enzymes is identified by three features:

1) molecular weight,

2) optimal activity range,

3) the known 20 amino acid fragment of the unknown amino acid sequence, SEQ ID NO: 1 and SEQ ID NO: 2.

However it appears that proteases a), b) and c) of claim 1 have to be isolated exactly how it was described in two publications quoted bellow. If the proteases are not isolated as described in the two publications quoted bellow they will be not the proteases used by the inventors, because the substance

called bromelain, or even stem bromelaine protease, is a very complex one. Thus, although the art of protein isolation and characterization is highly developed and skills of those in the art high, the proteins obtained with the same sample of proteins treated in different ways will differ depending on the methods used.

The one skilled in the art realizes that, for example, the molecular weight of a protein depends on the method used for its determination. The values 24.4 KDa, 24.5 KDa, 23.4 KDa recited by claim 1 were obtained by mass spectroscopy; see data for fractions F4, F5 and F9 in Harrach et al. (Isolation and Partial Characterization of Basic Proteinases from Stem Bromelain, Journal of Protein Chemistry, 1995, Vol. 14, 41-52. Harrach et al. indicate that, for example, F9 does not have the molecular weight of 23.4 KDa but 22.8 KDa when determined by SDS-polyacrylamide gel electrophoresis. Also the range of optimal pH activity of a protein depends on the substrate used. The ranges recited in claim 1 were obtained by Harrach et al. using L-pyroglutamyl-l-phenylanalyl-l-leucine-p-nitroanilide (PFLNA) as a substrate. With the other substrate the pH range might be different. The specification does not say that the quoted 20 amino acid fragments of the enzymes are the N-terminal. Therefore, one skilled in the art would not know how to sequence the isolated proteins to obtained SEQ ID NO: 1 and SEQ ID NO: 2.

In conclusion, without further guidance on the part of Applicants as to the details of the isolation of protease a), b) and c) the method of determination of their molecular weights and the ranges of optimal pH, as well as the way of sequencing, experimentation left to those skilled in the art has a low probability of success and is improperly extensive and undue.

The Applicants refer the one skilled in the art to two publications by the inventors. However, the attempt to incorporate subject matter into this application (page 5, line 9) by reference to:

Eckert et al., The Journal of Protein Chemistry 14, 1995, 41-52, (The first author on this paper is Harrach, not Eckert, see the copy included in IDS), and

Maurer et al. The Journal of Protein Chemistry 17, 1998, 351-361,

is improper, because the isolation, purification and characterization of fraction F4 (enzyme of claim 1 part a), fraction F5 (enzyme of claim 1 part b) and fraction F9 (enzyme of claim 1 part c) are essential to the instant invention. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing publication. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

In addition, claim 6 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 6 is directed to a medicament containing bromelain protease that is a recombinant protease of claim 1. The specification fails to disclose cloning and sequencing genes encoding proteases recited in part a), b) and c) of claim 1, the procedures necessary as the first step in obtaining these proteases in a recombinant form. Therefore, to make and use the claimed invention undue experimentation is necessary.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses cloning and sequencing DNA encoding three proteases isolated from so called stem bromelain protease originating from the plant of the family Bromeliacae. Although cloning and sequencing genes is a very well developed field and skills of artisans are high, the

experimentation required to make and use the claimed invention is out of the range of routine and tedious experimentation. The required experimentation includes:

i) translating SEQ ID NO: 1 and 2 into the nucleotide sequences,

ii) using the nucleotide sequences as primers in searching for the protease genes in the DNA of plants from the family Bromeliacae,

iii) expressing the candidate genes,

iv) testing the expressed proteins for features 1)-4) above,

v) selecting those that have all required features,

vi) transfecting the proper DNA molecules them into host cells, and

vii) producing the protein required for use in the claimed medicament.

The disclosure is silent about any of the outlined steps and experimentation being left to the skilled artisan has a rather low probability of success. Without further guidance on the part of applicants as to the sequence of the genes encoding protease of claim 1, as well as the plant of the Bromeliacae family to be used as a source of DNA, experimentation left to those skilled in the art is improperly extensive and undue.

3.3. 35 USC section 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 5 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Harrach et al. (Isolation and Partial Characterization of Basic Proteinases from Stem Bromelain, Journal of Protein Chemistry, 1995, Vol. 14, 41-52, included in IDS).

The claims are directed to a medicament, for inhibiting blood coagulation, consisting of bromelain protease of claim 1 part a).

The bromelain protease having properties as presented in claim 1 part a) is fraction F4 of stem bromelain isolated, characterized and partially sequenced by inventors in the publication by Harrach et al. that is incorporated into the specification by reference. In particular, bromelain protease of claim 1 part a) has a molecular weight of about 24.4 kDa; the same molecular weight is quoted by Harrach et all, page 47, left column, line 10. Bromelain protease of claim 1 a) has the optimal activity in the pH range of 4-5.5, which is the same as that of F4 given by Harrach et al. on page 50, left column, line 5. Bromelain protease of claim 1 a) comprises the amino acid sequence of SEQ ID NO: 1, which is contained in the amino acid sequence of F4; see Harrach et al. Table II page 48.

3.4. 35 USC section 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrach et al. (Isolation and Partial Characterization of Basic Proteinases from Stem Bromelain, Journal of Protein Chemistry, 1995, Vol. 14, 41-52, included in IDS) and further in view of Taussig et al. (Bromelain, the enzyme complex of Pineapple (*Ananas comosus*) and its clinical application. An update, Journal of Ethnopharmacology, 1988, 22, 191-203, included in the Information Disclosure Statement).

The claims are directed to the use of bromelain protease of claim 1part a) for inhibiting blood coagulation, wherein the plasmin production is stimulated, production of fibrin is inhibited and adhesion of thrombocytes on endothelium cells is inhibited.

Harrach et al. teach protease called F4 that is identical to protease of claim 1 part a); see the above rejection under 35 USC section 102. Harrach et al., however, do not teach that F4 has an inhibitory effect on coagulation of blood.

Taussig in his review teaches about use of bromelain in therapy of circulation diseases, page 194, paragraph entitled "*Circulation*". From this review one skilled in the art may learn that bromelain inhibits ADP-induced platelet aggregation (page 194, line 43 and further) and that as early as in 1979 Morita et al found that platelet aggregation inhibitory effect is connected with proteolytic activity of bromelain. On page 195, line 17, Taussig et al. teach about commercially available bromelain in the form of Anavit F3. Further Tausig writes "Several studies published in the late 1970s on the effect of bromelain on circulation, attribute its usefulness to activation of human plasminogen" (page 195, line 37) and on page 195, line 45, "Miyatani et al, (1975a) found that bromelain lyses fibrin the same way as plasmin and converts plasminogen to plasmin

as urokinase. Likewise, Livio et al. (1978), found bromelain to be an effective fibrinogenolytic agent both *in vitro and in vivo*, impairing coagulation of blood in rats."

It would have been obvious to one having ordinary skill in the art at the time of invention to have protease F4 isolated by Harrach et al. and use it for inhibition of blood coagulation as taught by Miyatani and Livio quoted by Taussig. The expectation of success was very high because F4 is one of eight proteases found in the stem bromelain. The motivation was also provided by Taussig in his review, because Taussig has presented evidence that bromelain is of high therapeutic importance in therapy of circulation diseases. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

4. Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

Art Unit 1652

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